REMARKS

Claims 1-31 are currently pending in the application. Claims 17-33 are withdrawn.

Sequence Compliance

The Office Action states that Applicant's response filed on September 13, 2004 did not contain a statement directing entry of the sequence listing into the specification. Applicants hereby request that the sequence listing filed on September 13, 2004 be entered into the above-captioned application.

Rejection Under 35 U.S.C. §112, First Paragraph

The Office Action states that claims 1-6 and 8-16 are rejected under 35 U.S.C. §112, first paragraph for alleged overbreadth. The Office Action states that while enabled for a method for preparing a cell line exhibiting constitutive hypermutation of a target nucleic acid region wherein said cell line is prepared from a B cell, the specification is not enabling for the method wherein the cell is other than a B cell. The primary rationale asserted in support of this rejection is that the specification does not teach practicing the method using any specific starting material, particularly in view of the assertion that at the time the instant application was filed, somatic hypermutation was identified as being restricted to B cells. Applicants respectfully disagree and traverse the rejection.

The standard for determining whether the specification enables the claimed invention is whether it would permit one of skill in the art to practice the invention without the need to resort to undue experimentation. The Office Action states that the specification teaches how to perform the claimed method using B cells as a starting material. It is important to note that the claimed invention is a method for preparing a cell line that includes screening a cell population for ongoing target sequence diversification. Thus, because the claimed method is adequately described where B cells are the starting material, then it is likewise adequately described where non-B cells are the starting material. One of skill in the art could simply run a cell of their choosing through the method and determine whether a cell exhibiting directed constitutive hypermutation is obtained. The fact that one of skill in the art may not have, as of the filing date,

been readily aware of other cell types that undergo directed constitutive hypermutation, does not mean that B cells are the only cell type that **can** undergo directed constitutive hypermutation. Thus, whether one of skill in the art knew, prior to performing the claimed method, whether a given cell type had the capacity for directed constitutive hypermutation, has no bearing on whether that skilled artisan would be able to follow the teachings of the specification and perform the claimed method to identify a cell line exhibiting directed constitutive hypermutation. That is, the specification teaches how to perform the method without undue experimentation regardless of whether the starting material (i.e., cell population) is capable of directed constitutive hypermutation. Moreover, the state of the art that has developed subsequent to the filing of the instant application supports the fact that the claimed method would, in fact, have identified non-B cell lines exhibiting directed constitutive hypermutation. For example, Morgan et al. (2004, J. Biol. Chem. 279:52353) teaches that activation induced cytidine deaminase (AID), an enzyme that has been shown in the art, not only to be required for somatic hypermutation (Neuberger et al., 2003 Trends Biochem. Sci., 28: 305; Honjo et al., 2002 Annu. Rev. Immunol., 20: 165), but to also have the ability to establish somatic hypermutation in cells that do not typically express AID (See, e.g., Yoshikawa et al., 2002 Science, 296: 2033; and Martin and Scharff, 2002 PNAS, 99:12304), has been identified as being expressed in oocytes, ovaries, embryonic germ cells, embryonic stem cells, and primordial germ cells. Given the expression of AID in these cell types, not only is it likely that these cells would undergo somatic hypermutation, but since they are pluripotent cell types, it is also likely that they may give rise to myriad cell types that express AID. While Applicants understand that enablement is judged as of the filing date, the post filing references merely indicate that one of skill in the art, practicing the invention as of the filing date, would have likely identified non-B cell populations exhibiting directed constitutive hypermutation.

The specification provides sufficient disclosure to permit one of skill in the art to practice the claimed method without resorting to undue experimentation, and Applicants accordingly request that the rejection be reconsidered and withdrawn.

The Office Action also states that claims 13-17 are rejected for alleged overbreadth because the specification does not provide enablement for the method wherein the rate of

mutation is modulated by expression of any sequence modifying gene product or any genetic manipulation. Applicants respectfully traverse the rejection.

Applicants note that claim 13 has been cancelled, thus the rejection is moot with respect to sequence modifying gene products. In addition, claim 1 has been amended to specify that the genetic manipulation is selected from gene deletion, gene conversion, or gene insertion. Support for this amendment is found on page 7, lines 4-6. Thus, claim 1 no longer reads on **any** genetic manipulation, but is instead limited to methods of genetic manipulation that were well within the grasp of one of ordinary skill in the art at the time the instant application was filed.

As amended, the claims are no longer overbroad, and Applicants accordingly request that the rejection be reconsidered and withdrawn.

Rejection Under 35 U.S.C. §112, Second Paragraph

The Office Action states that the claims are rejected under §112, second paragraph on several grounds.

The Office Action states that claim 1 is indefinite for failure to include an essential step relating to a step of determining the mutation rate. Claim 1 has been amended to remedy this deficiency. The Office Action states that claim 1 is also indefinite because the phrase "other nucleic acid" is not defined. Claim 1 has been amended and no longer recites "other nucleic acid." The Office Action also states that claims 2 and 6 are indefinite because they recite limitations as derivatives of some starting material. The claims have been amended to remove reference to derivatives. The Office Action also states that claim 6 is indefinite in the recitation "related to." Claim 6 has been further amended to delete the recitation of "related to." The Office Action also states that claim 14 is indefinite in reciting "one or more genes involved in DNA repair." Claim 14 has been amended to delete reference to genes "involved in" DNA repair. Claims 1-7 and 10-13 are also rejected for lack of antecedent basis. The claims have been amended to recite proper antecedent basis.

Applicants request that, in view of the amendments made to the claims, that the various rejections under §112, second paragraph be reconsidered and withdrawn.

Double Patenting

The Office Action states that the instant claims are rejected under the judicially created doctrine of obviousness type double patenting in view of co-pending application 10/146,505. Upon notification of allowable subject matter in the instant case, Applicants will timely file a terminal disclaimer effective to obviate the double patenting rejection.

Rejection Under 35 U.S.C. §102(b)

The Office Action states that claims 1-13 are rejected under §102(b) as anticipated by Sale et al. The Office Action states that Sale et al. teach each element of claim 1, with the exception of the requirement that the rate of mutation is modulated by genetic manipulation. The Office Action states that claim 10 of Sale et al. recites that the rate of mutation in the cell is modulated by administration of a mutagen, "which constitutes genetic manipulation of the cell." Applicants traverse the rejection.

Claim 1 has been amended to recite that the genetic manipulation is selected from gene deletion, conversion, or insertion. Sale et al. does not teach genetic manipulation by any of these means. Accordingly, Sale et al. fails to teach each element of amended claim 1, and therefore, does not anticipate claim 1. Each of claims 2-13 are directly or indirectly dependent from claim 1 and, thus, incorporate all the features of claim 1, including the recited modes of genetic manipulation. Accordingly, Sale et al. does not anticipate any claim depending from claim 1.

Because Sale et al. does not teach each limitation of the claimed invention, Applicants request that the rejection be reconsidered and withdrawn.

Applicant submits that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicant's attorney/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney/agent of record.

Respectfully submitted,

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